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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/822,975	04/12/2004	David A. Griffith	PC25409A	5681

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PFIZER INC.
PATENT DEPARTMENT, MS8260-1611
EASTERN POINT ROAD
GROTON, CT 06340

EXAMINER	
MOORE, SUSANNA	
ART UNIT	**PAPER NUMBER**
1624	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/21/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/822,975	GRIFFITH ET AL.	
	Examiner	Art Unit	
	Susanna Moore	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 December 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) *1-97* is/are allowed.

6)☒ Claim(s) *98-103,105-115 and 117-123* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 1-103, 105-115 and 117-123.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group I, claims 1-17(part), 18, 19-24(part), 25, 26-32(part), 33, 34-39(part), 40, 41-46(part), 47, 48-53(part) and 54-123, pyrazolopyrimdines, in the reply filed on 12/14/2006 is acknowledged. Note, the restriction requirement was not between products and the process of using said products. The restriction requirement was made between products based on the classification of said products, and as such, is proper and **Final**.

Claim Rejections

Claim 123 is rejected as drawn to an improper Markush group, as this claim contains both elected and non-elected subject matter, which are parts of different inventions. The choices are not art-recognized equivalents for reasons set forth in the requirement for restriction. Deletion of non-elected subject matter will overcome the rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 98, 103, 109, 115 and 120 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The terms "analog" or "analog thereof" are indefinite. What are these analogs of leptin and dehydroepiandrosterone?

Applicants argue, "Ananlogs of Leptin and dehydroepiandrosterone (DHEA) are well known to those skilled in the art. Examples of Leptin analogs include LY355101 and LY396623 (Eli Lily & Co.). Examples of DHEA analogs include 16a-fluoro-5-androsten-17-one (fluaterone) and immunor (IM28)."

While these are some examples of analogs of leptin and dehydroepiandrosterone, these are not the only analogs. The scope of Applicants claims are not limited to those analogs found in the reference provided, and as such, the term "analog" should be removed from said claims. Applicants have not shown where the line is between "analog" and those a little too far removed to be called analogs.

Claims 107-110 and 118-122 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "pharmaceutical agent" is vague. Agent for what? What are these pharmaceutical agents? Are these preservatives? Maybe surfactants? What does Applicant intend? Is this supposed to cover all drugs?

Applicants point out on page 26 of the Specification, pharmaceutical agents are defined. But the Specification uses open-ended language, i.e. "preferred agents include." What pharmaceutical agents are not included? Which are not preferred? The "...include" is not a definition or in any way limiting.

Claims 99-103, 105-115 and 117-122 are rejected under 35 U.S.C. 112, first paragraph, because the Specification, while being enabling for treating smoking cessation, obesity and bulimia, does not reasonably provide enablement for treating any of the other specifically listed diseases whose treatment is claimed.

Claims 99-103, 105-115 and 117-122 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Such a utility cannot be deemed enabled.

Pursuant to *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), one considers the following factors to determine whether undue experimentation is required: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of

direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. Some experimentation is not fatal; the issue is whether the amount of experimentation is "undue"; see *In re Vaeck*, 20 USPQ2d 1438, 1444.

The analysis is as follows:

(A) Breadth of claims.

(a) Scope of the compounds. The instant claim embraces millions of compounds with a pyrazolo[4,3-d]pyrimidine framework with a variation of substituents at four different positions. These variations to the scaffold give a diverse range of compounds, which provide different physical and chemical properties to the compounds of formula (I).

(b) Scope of the diseases covered. Claims 99-122 are drawn to a method of treating (I) weight loss, (II) obesity, (III) bulimia, (IV) depression, (V) atypical depression, (VI) bipolar disorders, (VII) psychoses, (VIII) schizophrenia, (IX) behavioral addictions, (X) suppression of reward related behaviors, (X) alcoholism, (XI) tobacco abuse, (XII) dementia, (XIII) seizure disorders, (XIV) epilepsy, (XV) attention deficit disorders, (XVI) Parkinson's disease, (XVII) inflammation, (XVIII) gastrointestinal disorders and (XX) type II diabetes. The scope also covers a condition or disorder which is modulated by a cannobinoid receptor antagonist, for which there is no standard list. The scope of some of the "umbrella" terms will be discussed below.

(I) Weight loss, in the context of medicine or health, is a reduction of the total body

weight, which can mean loss of fluid, muscle or bone mass, or fat. Weight loss can unintentional, e.g. a side effect of medication, or intentional in an effort to improve fitness, health, and/or appearance.

(X) Suppression of reward related behaviours is associated with the *pleasure system* of the brain, providing feelings of enjoyment and reinforcement to motivate a person proactively to perform certain activities. Nuerotransmitters are released (particularly in areas such as the nucleus accumbens and striatum) by naturally rewarding experiences such as food, sex and socializing.

(XIII) Seizures are temporary abnormal electro-physiologic phenomena of the brain, resulting in abnormal synchronization of electrical neuronal activity. They can manifest as an alteration in mental state, tonic or clonic movements, convulsions, and various other psychic symptoms. They are due to temporary abnormal electrical activity of a group of brain cells. The medical syndrome of recurrent, unprovoked seizures is termed epilepsy, but some seizures may occur in people who do not have epilepsy. Seizure is often associated with a sudden and involuntary contraction of a group of muscles. However, a seizure can also be as subtle as marching numbness of a part of body, a brief loss of memory, sparkling or flashes, sensing an unpleasant odor, a strange epigastric sensation or a sensation of fear. Therefore seizures are typically classified as motor, sensory, autonomic, emotional or cognitive. These include absence, myoclonic, clonic, tonic, tonic-clonic, and atonic seizures.

(XVII) Dementia is the progressive decline in cognitive function due to damage or disease in the brain beyond what might be expected from normal aging. Dementia is a non-specific term that encompasses many disease processes, just as fever is attributable to many etiologies, e.g. Alzheimer's disease, vascular dementia (including Binswanger's disease), dementia with Lewy bodies, frontotemporal lobar degeneration (FTLD, including Pick's disease), frontotemporal dementia, semantic dementia, progressive non-fluent aphasia, Creutzfeldt-Jakob disease, Huntington's disease, Parkinson's disease, HIV infection, head trauma, hypothyroidism, vitamin B1 (thiamine) deficiency, Vitamin B12 deficiency, Vitamin A deficiency, depressive pseudodementia, normal pressure hydrocephalus and tumors.

(XVI) Parkinsons disease is a degenerative disorder of pigmented dopamine-secreting (dopaminergic) cells and subsequent loss of melanin, secreted by the same cells, in the pars compacta region of the substantia nigra of the brain. This is characterized by muscle rigidity, tremor, a slowing of physical movement (bradykinesia), and in extreme cases, a loss of physical movement (akinesia). The primary symptoms are the results of excessive muscle contraction, normally caused by the insufficient formation and action of dopamine, which is produced in the dopaminergic neurons of the brain.

(XVII) Inflammation is the body's first response to injury, e.g. trauma, infection irritation, etc. This is a non-specific immune response. An inflammatory disease can be characterized by the following: redness, heat, swelling, pain, and dysfunction of the organs involved. Some examples of inflammatory diseases are as followed, but not limited to: allergies, appendicitis,

arteritis, arthritis, asthma, blepharitis, bronchiolitis, bronchitis, bursitis, cervicitis, cholangitis, cholecystitis, chorioamnionitis, colitis, conjunctivitis, cystitis, dacryoadenitis, dermatitis, dermatomyositis, encephalitis, endocarditis, endometritis, enteritis, enterocolitis, epicondylitis, epididymitis, fasciitis, fibrositis, gastritis, gastroenteritis, gingivitis, hepatitis, hidradentitis supparativa, ileitis, immune reconstitution inflammatory syndrome (IRIS), laryngitis, mastitis, meningitis, myelitis, myocarditis, myositis, nephritis, omphalitis, oophoritis, orchitis, osteitis, otitis, pancreatitis, parotitis, pelvic inflammatory disease (PID), pericarditis, peritonitis, pharynx, pleuritis, phlebitis, pneumonitis, protitis, prostatitis, rhinitis, salpingitis, sinusitis, stomatitis, synovitis, tendonitis, tonsillitis, uveitis, vaginitis, vasculitis and vulvitis.

(XVIII) Gastrointestinal disorders can be defined as any disease or disorder associated with the GI tract, which include the mouth, esophagus, stomach, intestines, rectum and anus, as well as the spleen, bile ducts, gall bladder, liver and pancreas. As recited, the scope of the claim can include, but is not limited to, tooth decay, periodontal disease, abscesses, canker sores, cold sores, oral cancer, gastroesophageal reflux disease, dysphagia, esophagus cancer, circopharyngeal incoordination, achalasia, diverticula, burning mouth syndrome, pancreas cancer, Crohn's disease, colon polyps, diverticular disease, intestinal parasites, salivary gland disease, sialhorria, dentigerous cyst, glossitis, benign migratory, Ludwig's Angina, Melkerson-Rosenthal Syndrome, xerostamia, Pierre-Robin Syndrome, diabetes, lactose intolerance, bruxism,ulcerative colitis, cystic fibrosis, pernicious anemia, tropical sprue, cirrhosis, Bassen-Kornzweig syndrome, pancreatitis, Shwachman-Diamond syndrome, anal cancer, acute pancreatitis, anal fissure, anal fistula, colorectal cancer, hemorrhoids, perirectal abscess,

proctitis, rectal prolapse, functional constipation, liver cancer, diarrhea, ankyloglossia, Irritable Bowel Syndrome, functional dyspepsia, peptic ulcer, intussusception, Coeliac disease, Whipple's disease, lymphoma, incontinence, chronic pancreatitis, Hirschsprung's disease, infant regurgitation, biliary disorder, hemochromatosis, Wilson disease, tyrosinemia, alpha 1 antitrypsin defiency, glycogen storage disease, primary sclerosing cholangitis, hepatitis A, hepatitis B, hepatitis C, Reyes's syndrome.

These are just some of the diseases embraced by the scope of claims 99-122.

(B) The nature of the invention and predictability in the art: The invention is directed toward medicine and is therefore physiological in nature. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(C) Direction or Guidance: That provided is very limited. The dosage range information, found on page 49 of the Specification gives 0.7-7,000 mg/kg, which is very broad. Moreover, this is generic, the same for the many disorders covered by the Specification. Thus, there is no specific direction or guidance regarding a regimen or dosage effective specifically for any and all diseases encompassed by the scope of claims 99-122.

(D) State of the Prior Art: These compounds are substituted pyrazolo[4,3-d]pyrimidine with a substitution pattern at four positions. So far as the examiner is aware, no substituted

pyrazolo[4,3-d]pyrimidine of any kind have been used for the treatment of any and all the diseases encompassed by the scope of claims 99-122.

(E) Working Examples: The invention is drawn to the therapy of all the diseases listed under the Scope of diseases. There are several prophetic in vitro assays, including inhibition assays of human and rat CB1 and CB2 assays and activation assays, including GTPγ assay, FLIPR-based assay, and c-AMP assay. There are several prophetic in vivo assays drawn to locomotor activity, catalepsy, hypothermia, hot plate, food intake, alcohol intake and oxygen consumption. There are no working examples or data in the Specification drawn to this utility to support the use of substituted pyrazolo[4,3-d]pyrimidine to treat any or all the diseases covered by the Scope of diseases.

(F) Skill of those in the art: These diseases and disorders cannot be treated generally by any one drug. These are all different diseases and disorders, which occur at different locations and by different modes of action in the body. Hirschsprung's disease, one of the many mentioned above, is a disorder, which is primarily treated with surgery. The instant compounds, substituted pyrazolo[4,3-d]pyrimidine, are recited as useful in treating any or all functional gastrointestinal disorders, for which applicants provide no competent evidence. Coeliac disease is untreatable. Hepatitis is treatable with antiviral agents, a property these compounds not disclosed to have.

Obesity, a condition which is just the opposite of weigth loss, is not treated with the same pharmacotherapy as weight loss. They are at opposite ends of eating disorders.

Enablement for the scope of"treatment of inflammation" generally is not present. For a compound or genus to be effective against inflammation generally is contrary to medical science. Inflammation is a process, which can take place individually any part of the body. There is a vast range of forms that it can take, causes for the problem, and biochemical pathways that mediate the inflammatory reaction. There is no common mechanism by which all, or even most, inflammations arise. Mediators include bradykinin, serotonin, C3a, C5a, histamine, assorted leukotrienes and cytokines, and many, many others. Accordingly, treatments for inflammation are normally tailored to the particular type of inflammation present, as there is no, and there can be no "magic bullet" against inflammation generally. Hence, some types of inflammations are treated with antibiotics. Certain types of anti- inflammatory agents, such as non-steroidal anti-inflammatory medications (Ibuprofen and naproxen) along with muscle relaxants can be used in the non-bacterial cases. This helps establish that it is not reasonable for any agent to be able to treat inflammatory disorders generally.

To date, there are no CB1 antagonists used to treat Parkinson's disease patients or dyskinesias. Note that Parkinson's disease itself is not treatable, current therapies are directed only to symptom alleviation.

Note that many of the diseases listed in the Scope of diseases are “umbrella” terms that are very broad in scope. Such as dementia, most forms are untreatable. All forms of seizures are covered by the Scope, even those seizures that have nothing to do with the cannabinoid receptors.

Applicants point out the 40 literature references cited in the IDS pertaining to the therapeutic value of the instant compounds, but Applicants have not pointed to where this teaching is present in the document. When applicants cite a multi-page document without citing a specific portion or page, the examiner will not pour over the document to extract the relevant information. See *Clintec Nutrition Co. v. Baxa Corp.*, 44 USPQ2d 1719, 1723 n.16 and *DeSilva v. DiLeonardi*, 181 F.3d 865, 866-67 (7th Cir. 1999). This is expecially true when Applicant is pointing to dozens of references.

As for the three references cited on the second page of the Remarks, these references will be addressed individually below.

Adams et. al. (Expert Opin. Ther. Patents, 2002) provides an review of the patents which covers from January 2000 to July 2002. Keep in mind, this is a review of patents submitted, that may or may not, have the required pharmacological assays which correlate to the disclosed treatment of diseases. Section 3, pages 1482-1484, provides the review for the cannabinoid receptor antagonists, the mode of action Applicants disclose. Most of the examples provide binding assays, which is not the issue at hand. Applicant is enabled for the antagonistic activity at the cannabinoid receptors. The focus is on the treatment of the many diseases Applicants is claiming the correlation of those diseases with pharmacological assays. There is very little provided on the treatment of any diseases. The following examples are the few mentioned.

One such example, SR141716A, which is not embraced by Applicants claims, is in phase II clinical trials for the treatment of obesity and showed significantly reduced body weight in obese patients when compared to a placebo. See page 1482, right-hand column, lines 1-5.

SR141716A was tested for treatment of a certain neuroinflammatory pathology. The compound was assessed in vivo models of experimental allergic encephalomyelitis (EAE). This

is far narrower than inflammation, most of which are not neuroimflammation.

In the second model, the EAE model is stated to be a model of CNS autoimmune and inflammatory disorders brought about by demyelinated lesions exemplified by sclerosis of plaques in humans. Again, this covers just a very specific form of inflammation.

Sanofi-Synthelabo also claims the use of SR141716A to facilitate smoking cessation. Patients receiving SR141716A showed improved abstinence in comparison with the placebo group.

The second reference, Mackie (Annu. Rev. Pharmacol. Toxicol.) is a 2006 article, two years after Applicants effective filing date. This article will not be considered since it does not meet the state of the art at the time the instant Application was filed.

The third reference, Pertwee et. al. (Prostaglandins, Leukotrienes and Essential Fatty Acids, 2002) is an overview of the canabinoid receptors and does not provide much information on the treatment of diseases. There is one short section on page 114 and 115 (bridged). On page 114, right-hand column, last paragraph, it states, "Several therapeutics have been suggested for CB1 receptor antagoniss/inverse agonists." In the same paragraph, the third line from the bottom of the page says, "...they may have therapeutic potential as..." The words "suggested" and "may have" are not evidence of enablement but in fact point against it. If something is merely a "suggested" it is not yet enabled.

To address some of Applicants remarks concerning treating many diseases with one drug

through different modes of actions. Yes, it is true some drugs can treat more than disease or symptoms of a disease. But there is no real evidence that one drug that hits many different targets and pathways is capable of treating different diseases that are not related.

Applicants also state, "Treatment of diseases and disorders include the treatment of the symptoms." While this is true, when claiming the treatment of a particular disease, Applicant is claiming the treatment of the disease itself, not merely its symptoms.

(G) The quantity of experimentation needed: Owing especially to the factors of A, C, E and F, the amount of experimentation is expected to be high.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susanna Moore whose telephone number is (571) 272-9046. The examiner can normally be reached on M-F 8:00-5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Wilson can be reached on (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

SM

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